Memo

date: October 24, 2001

to: Barry Cherney, Ph.D., Deputy Director, DTP, OTRR, CBER, FDA
Amy Rosenberg, M.D., Director DTP, OTRR, CBER, FDA

cc: Gibbes Johnson, Ph.D., (BLA STN 125029 Committee Chairman)
DTP, OTRR, CBER, FDA

from : Frederick C. Mills, Ph.D.
Staff Scientist, DTP, OTRR, CBER, FDA

subject : CM & C review of BLA STN 125029
recombinant human activated protein C (rhaPC)
Sponsor : Eli Lilly
Indication: severe sepsis

Summary
The following subjects are included in this review:

1. Raw Materials used in the Manufacture of rhaPC Drug Substance (including the control of animal-derived raw materials)
2. Production Construct
3. Cell Banks
4. Drug Substance Manufacturing from Initial Culture Seed to Supernatant Harvest
5. Drug Substance Stability
6. Drug Product Manufacturing
7. Drug Product Stability
8. Drug Product Methods

The other CM & C aspects of the BLA were reviewed by Gibbes Johnson (Drug Substance Manufacturing and Methods), Rona LeBlanc (Viral Clearance and Viral Validation), and Gary Kikuchi (Immunogenicity)

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1. Raw Materials used in the Manufacture of aPC Drug Substance

Raw materials are typically accepted on the basis of a Certificate of Analysis (COA) and, at a minimum, an in-house identification test, unless otherwise noted. In-house testing is performed by ----------. There are three categories of raw materials: purchased, custom, and manufactured in house

a. Raw materials used in the manufacture of the MCB and WCB

Purchased Raw Materials

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Significant analytical properties of these reagents and the limits on these properties from both the vendors and ---------, provided in tabular form for all of these reagents except ----------.

This documentation is satisfactory

Custom Manufactured Raw Materials

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Specifications, analytical properties, and limits from both ---------- and -------- are supplied. This vendor is subject to audit by Lilly and/or ----------

This documentation is satisfactory.

Manufactured Raw Materials

---------- Media for Cell Bank*

---------- Media

---------- Solution

Deionized Water

Water for Injection (WFI)

Specifications are provided for the ----------, and ----------solution. These media are not routinely tested. The Deionized water and WFI meet USP criteria.

Reviewer's comment
--------- should commit to testing ---- medium and the ---------- solution. This issue was raised in the September 21, 2001 CM & C DR letter, and Lilly responded in Amendment 24 to the BLA. (see Questions and Requests for the Manufacturer at the End of this Review)

Certificates of Analysis
Certificates of Analysis are provided for the raw materials that are accepted on the vendor Certificate of Analysis (provided as scanned images) and a minimum of an identity test (where available) is performed by ----------.,
This documentation is satisfactory

b. Raw Materials Used in Cell Growth and Harvest/Recovery

Purchased Raw Materials
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Geneticin (Geneticin Sulfate, ------)
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Significant analytical properties of these reagents and the limits on these properties from both the vendors and ---------, provided in tabular form, except for ----------
[
] for which only -
------- analytical properties and limits are tabulated.
This documentation is satisfactory

Custom Manufactured Raw Materials
Hydrated Liquid Perfusion Media (---------) *This media appears to be made by -------, but this is not clearly indicated on COA*
---------- Media ----------
---------- Media *The source is not clearly indicated on COA*
Specifications, analytical properties, and limits for these properties are supplied for these media. Both vendor data and -------- data are supplied. These vendors are subject to audit by either Lilly and/ or ----------

Reviewer's comment
Lily must specify the manufacturers of ---------- media. This issue was raised in the September 21, 2001 CM & C DR letter, and Lilly responded in Amendmnt 24 to the BLA. (see Questions and Requests for the Manufacturer at the End of this Review)

Manufactured Raw Materials
---------- Solution
---------- Solution
---------- Solution
---------- Media (----------)*
---------- Solution
Media for Seed Fermenter (----------)*
---------- Solution
---------- Solution
---------- Solution
---------- Stock Solution
Deionized Water
Water for Injection

---------- solution are not routinely tested. Specifications, analytical properties, and limits for these properties are supplied for the other reagents.

Certificates of Analysis
Certificates of Analysis are provided for the raw materials that are accepted on the vendor

Certificate of Analysis (provided as scanned images) and a minimum of an identity test (where available) is performed by ----------.,
This documentation is satisfactory

c. Raw Materials Used in the Purification Process

Purchased Raw Materials

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Significant analytical properties of these reagents and the limits on these properties are in provided in tabular form-for instance
[

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---------- are tested at ----------.and meet tests of Ph.Eur and USP. For ----------data from the vendor as well as results of -------- tests are supplied. For ----------, only vendor data is supplied.

This documentation is satisfactory

Custom Manufactured Raw Materials

The only custom manufactured raw material used in purification is -------- thrombin, which is used to activate the protein C holenzyme to aPC. The manufacture of this item is per specifications from Eli Lilly and Co., and is subject to audit by either Eli Lilly and/or ----------. As per ----------, this is New Zealand or US –sourced. Also viral tested as per 9CFR This reagent is discussed more fully below in a separate section on Control of Animal Derived Raw Materials.

Manufactured Raw Materials and Buffers

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--------- data for significant analytical properties of these reagents and the limits on these properties are in provided in tabular form. The --------- ppm ----------is not routinely tested. This documentation is satisfactory

Certificates of Analysis

Certificates of Analysis are provided for the raw materials that are accepted on the vendor Certificate of Analysis (provided as scanned images) and a minimum of an identity test (where available) is performed by ----------.,

This documentation is satisfactory

Control of Animal Derived Raw Materials

Lilly addresses the concerns around Bovine Spongiform Encephalopathy (BSE) by providing diligent control of raw materials to assure minimal risk of the agent causing BSE. The Lilly corporate policy is to remove, whenever possible, any animal-sourced material in the development, production or purification of its pharmaceuticals. In the case of rhAPC, the use of

certain bovine-derived materials in the production and purification of the protein is considered crucial. These bovine materials include ---------- ---------- which is derived from bovine ----------. In addition, ---------- is used in the media-fill validation at the contract facility (----------) where rhAPC is compounded into the drug product.

Guidelines approved in both Europe and the United States regarding BSE were consulted in determining the strategy utilized to address animal derived raw materials in the manufacture of the active (drug) substance. To guarantee the use of BSE free material Lilly requires the vendors to source animals from non-BSE countries. The following is a brief summary of the strategy employed.

1. Lilly has identified all ruminant-derived raw materials used in the manufacture of the drug substance and drug product. These include raw materials used in the production, purification, formulation, and filling operations. As mentioned above, only four raw materials have been identified that contain animal-sourced material. The following is a brief synopsis of the bovine materials and their use in the manufacture of rhAPC.

a. Fetal bovine serum from ---------- (----------) was used in the preparation of the master and working cells banks.
b. ---------- from either New Zealand (----------) or the USA (----------) is used in the pre-culture for cell culture of ---------- cells.
c. ---------- is used in the cell culture of ---------- cells, is derived from USA cattle.
d. ---------- from bovine ---------- , is used in the ---------- ---------- and may be from either New Zealand or USA cattle.
e. ---------- derived from bovine ------ and is used as a growth indicator for validation of the media fill line. This material is derived from USA cattle.

2. Lilly has conducted vendor audits of the suppliers of the bovine-derived raw materials (See Additional Information on Bovine-Sourced Material from the -------- PAI- below). All bovine raw materials will be obtained from animals born and raised in the either the USA or New Zealand, both of which have notification systems for BSE. Abattoirs that are the source of the bovine raw material maintain records that certify the country of origin of the animal used in the production of the raw materials. In addition, the serum and tissue will only be processed in equipment that has not processed tissue or serum from animals originating in countries other than the USA or New Zealand. The serum or plasma and tissue used for the production of the biological reagents is listed as Category IV (no detectable infectivity) as per the document “Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Medicinal Products” (CPMP/BWP/877/96). The serum\plasma is collected in such as manner as not to present a hazard of cross-contamination with neurological tissue.

3. On file at the vendors for each lot of bovine raw material is a veterinary report from the countries respective veterinary regulatory authorities stating the country of origin of the live animals.

4. As part of Lilly's routine production, records will be maintained on each lot of rhAPC drug substance and drug product regarding the source of the ruminant derived raw materials.

---------- used in the cell bank was derived from human hair and/or chicken feathers, although a non-animal derived -------- was subsequently identified and is used in the production process. Since -------- is produced using very high temperatures and highly acidic hydrolysis conditions, designed to effectively convert the ----------, use of this material in the cell bank does not represent a significant risk factor for the product.

The vendors of ruminant-derived raw materials have also obtained Certificates of Suitability as prescribed in the Council of Europe, European Directorate for the Quality of Medicines (EDQM). These certificates are designated as Certification of Suitability to the Monograph of the European Pharmacopoeia - "Products with risk of transmitting agents of animal spongiform encephalopathies. EDQM certificates of suitability are valid for five years, provided there is no change in manufacturing procedure, country of origin, or nature of tissues used. Moreover, there can be no deterioration in the TSE status of the country of origin for the source material. Copies of Certificates received as of December 15, 2000 were included in the BLA.
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Additional information on Bovine sourced material from the ---------- PAI.

During the PAI of the ---------- May 30-June 8, 2001, additional information was provided on the suitability of ruminant derived material used in manufacture of the drug substance. This information included a summary of the February 22-25, 1999 audit of ---------- facilities in ----------, ---------- performed by Lilly personnel (----------) ---------- supplies ----------and ---------- for aPC production. The Lilly audit focused on ---------- production, and the results of the audit were submitted to the Council of Europe, European Directorate for the Quality of Medicines (EDQM), which then supplied a Certification of Suitability as described above. The ---------- certificate, which was not in the BLA, was given to FDA inspectors during the PAI.

---------- is an alternate supplier of thrombin, so an audit was conducted by Lilly personnel (----------, lead auditor) of ----------) plant on February 27, 2001. Because ---------- lot release testing is conducted at ----------, facility, this facility was also audited at the same time. As per the other audits, data was submitted for to the EDQM, which after review supplied a Certificate of Suitability for ----------, and this was supplied to the FDA during the ------- PAI.

During the PAI, a summary was supplied for the March 27-28, 2000 audit of the ---------- production facility in ----------, conducted by ----------personnel (----------. Because this audit was conducted during autumn in ----------, no ---------- were being harvested, but ---------- records and facilities were inspected, and personnel were interviewed. As was the case with the -------- audit, data was supplied to the EDQM, which then supplied a Certificate of Suitability for ----------. This Certificate, which was also not in the BLA, was given to FDA inspectors during the PAI.

It was stated during the PAI --------- and Lilly are planning yearly audits of the ----------and ---------- suppliers.
Reviewer's comment: ---------- and Lilly are maintaining adequate control over the sourcing of animal derived materials.

2. Derivation of rhaPC Production Constructs

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The final production plasmid is ---------- (shown below). The multi-step derivation of this plasmid is adequately described.

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Lilly has provided extensive schematics, figures, and verbal explanations for the production of the production plasmid ----------. The important functional units in these plasmids were sequenced. The description and characterization of the production constructs is adequate.

Preparation of the Production Cell Line

The human ------ parent cell line, into which the Protein C expression vectors were introduced, is a permanent line of primary human embryonic kidney. The cell line was isolated in 1973 by *in-vitro* transfection of human ----------. The method of cell transformation ----------. An analysis by cloning and sequencing of the cellular-viral junctions has revealed that the ---------- cell line contains the fragment ----------. The ---------- originally used to transform the cell line is classified as a ----------.

There is no known information on the medical history of the donor. However, extensive biosafety testing has failed to identify any evidence for the presence of adventitious agents in the recombinant derivatives of this cell. (*Dr. LeBlanc's review*)

Discussion follows of the post-translation modifications, including ---------- in the ---------- that is necessary for efficient secretion. Lilly had difficulty in identifying a cell line that gave efficient secretion. It was discovered that an ---------- was capable of producing fully active human Protein C (----------). The fact that the parent -----cell line is adenovirus-transformed is itself important to the processing. Lilly found that the ---------- transformation of a cell is critical for the secretion of highly functional, correctly modified protein, partly because of ----------). The adenovirus E1A gene product is also

necessary for activity of the ---------- present in the ---------- expression constructs (see Construct section –above).

Selection and Cloning of Production Cell Line

---------- of the ------cell line yielded a clone designated ------. It was determined that rates of secretion higher than those obtained in clones such as -------- apparently were not possible due to a limitation in ----------. Therefore, ------- was further selected for PC production to yield a clone with ------ fold higher secretion, designated ---------- was re-transfected with --------, and the transfectants selected with G418. ----------. A clone designated --------- was selected. By selecting a line ---------with improved secretion, stable, nonamplified subclones capable of producing recombinant human Protein C at commercially viable levels were re-isolated. Protein C produced from the high-producing recombinant ------cell line was fully processed and fully functional, as determined by *in-vitro* anticoagulant activity.

Description of the Cell Line

Both the ------- and -------- research cell lines were tested for the presence of adventitious agents. The state of the expression vectors in the cell lines were characterized. ---------has copies of ---------- integrated at --- sites, and ----- has copies of -------- --integrated at ----------. The integrity of the expression construct in the MCB was determined by several techniques, ----------

There are ---------- copies of PC coding sequence in ----------, calculated on the basis of a triploid cell.

For production and post production cells, ---------- analysis was performed along with ---------- to confirm that the mRNA being produced by the cell and coding for the secreted Protein C was intact, with no insertions or deletions.

Cell Banks

---------- different sets of Master Cell Banks (MCB) and Working Cell Banks (WCB) have been prepared. ----------MCB and ---------- WCB) was generated in 1991 and was used in the manufacture of ----- and ------. The ---------- MCB and ----------, WCB) was generated in
1998. The ---------MCB and WCB were prepared from a subclone of ----------. This new subclone was designated ----------, and was used to generate the MCB and WCB from which ---------- and Commercial material have been produced.

The rationale for the subcloning of ---------- is summarized below:

•It was an expectation of draft guidances proposed in the mid 1990's that producer cell lines should be subjected to at least one well-documented single cell isolation based cloning immediately before cell banking and manufacture of a Master Cell Bank (MCB) and Working Cell Bank (WCB).
•The additional subcloning was done to further increase the assurance that the cell line used in the late Phase III clinical trials and for commercial production was derived from a single cell.
•The WCB---------- was established using ----------, whereas the MCB---------- was established using ----------. Therefore, the
new MCB (----------) and WCB (----------) was subcloned
from the WCB, ---------- thereby, eliminating the ---------- present
in the original MCB.

•The original MCB and WCB used ----------, which was replaced in the new MCB (----------) with the ----------.

A history of cell banks leading to the ---------- Master Cell Bank is provided. The new MCB and WCB were created at ----------.

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Security Measures for the Cell Banks

During the ----------PAI inspection, a review of Cell Bank security was performed. ----------generated the existing MCB and WCB in 1998, and ---------- maintains the original documentation for the Cell Banks. An ID code for Cell Banks is issued by ----------. When Cell Banks are transferred to the ---------- facility, there is a protocol that requires ---------- sign-out, and ----------sign-in , with one witness required for the sign-in. There is no routine temperature monitoring of the shipping containers during ----------to ---------- transfer. ------of the MCB is maintained at the Lilly---------- facility, and ------of the MCB is maintained at ----------. Further WCB vials will be generated at ---------- as necessary.

At ---------- the rhaPC MCB and WCB are kept in a locked room, with access controlled by QC supervision. The rhaPC Cell Banks are kept in a ----------, in a tray reserved for this product. -------- maintains Cell Banks for its other contract products on additional trays in this ----------. The -------- is required to have an ---------- depth of ----------, and this storage facility has an emergency power backup. The Batch record contains a dispensing sheet for sign-out. At the start of a Batch production, only one WCB ampule is signed out, and is carried on -------- to the ---------- facility.

Satisfactory security, geographic separation, and sign-out procedures are maintained for the Cell Banks. The issue of routine temperature monitoring for transfer of cell banks from -------- -- to -------- ----------h was addressed via two teleconferences on October 19, 2001 (Excerpted from the EIR for the -------- facility inspection).

The first teleconference was initiated at 10:10 A.M by myself and Laurie Norwood, in a call to ----------. I asked ---------- to confirm that there is in fact no routine temperature monitoring of the cell banks that are shipped from -------- --. ---------- responded that she thought this was the case, and wondered how one would monitor temperature, since the cell bank ampules are shipped in ----------. Laurie Norwood agreed that there is probably no way to monitor temperature in ----------, and asked whether there was shipping validation for this transport step, and also if the ---------- level was checked upon arrival to -------- -----

----------. ---------- responded that -------- has performed shipping validation for this step, and that there is a procedure for checking the state of the ---------- in the shipping container. Laurie Norwood asked if the specifics for shipping validation and receipt of the cell banks could be provided. ---------- responded that she would need to discuss the issue with ----------, and that she would call back within an hour.

---------- initiated the second teleconference at 11:20 A.M. and communicated the following information to me regarding shipping validation for -------- --- to -------- ---------- transport, as well as the SOP for receiving cell banks at -------- ---.

1. Shipping validation
This was done under Protocol ----------. This was a validation for three days' shipping time. The shipping time from -------- --- is ----------. ----------. The results of this validation support a ---------- day shipping time.

2. [

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This communication was judged by myself and Laurie Norwood to provide a satisfactory resolution of this issue.

Testing and In-Process Controls of the Master Cell Bank

Extensive characterization and testing for adventitious agents was performed on both the -------- MCB from 1991, and the ---------- cell bank, derived in 1998 at -------- --- by ---------- from the --------- WCB. These tests were performed by ---------, and ---------- assay numbers are supplied.

Result of analysis for the ------MCB are summarized in the following tables

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Cell line characterization on ------was consistent with cells of human origin, and ----------. As expected for cells able to grow ----------, these cells formed ---------- and also formed ----------. Tests for bacterial, fungal and mycoplasma contaminants were negative. Extensive viral characterization was performed and yield no evidence of viral contamination of this MCB (reviewed by Rona LeBlanc). It is significant that the MCB is negative for ---------- since the parental ---------- cells were transformed with ----------, and with the exception of ----------, the ---------- cell line will support the growth of all known types of human ----------

The results of ---------- tests on the ---------- MCB, which is used in the current production, are shown below.

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---------- MCB cells showed an ---------- typical of human cells, and was negative for bacteria, fungal, and mycoplasma contamination,. Extensive viral testing, including ----------, was negative.

Preparation and Control of Working Cell Banks

A new WCB was derived from the ---------- Master Cell Bank at ----------. Results of characterization assays are presented above in Table I.C.8, showing that the new WCB has a human ----------, and is negative for bacterial, fungal and mycoplasma contamination, contains to identifiable retroviral particles or RT activity, and does not produce ---------- with a battery of viral assay

cell lines. The protocol for production of ---------- Working Cell Banks at -------- --- is described. A new WCB batch will consist of ---------- vials will be filled with ---------- ml of ----------, and will contain ----------. The following assays to be performed on the WCB batches.
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These tests will include in-vivo viral assay, which were not performed on the WCB batch made in 1998.

Preparation and Testing of Cells at the Limit Of In-Vitro Age for Production

As recommended by ICH Q5 guidance, testing of production cells at the limit of in-vitro age was performed. These studies were done at Lilly, ---------- facility with a ------L bioreactor. The following limitations are in place for the number of generations: The cells cannot be seeded into the inoculum bioreactor (---------- if more than --- generations have passed, counting from the ---------- cell bank. The cells cannot be older than --- generations before being seeded into the production bioreactor (----------). These limitations in age were decided upon based on laboratory evaluations of growth and productivity (----------) over --0 generations.The limitations for the time is valid for the production process in the ---------- L production bioreactor. The limitation is that the

production process will be terminated before --- days have elapsed from seed of the production bioreactor. Most of the production runs are terminated at the age of approximately --- days. All of the pilot plant runs producing clinical trial material followed this limitation, except the ones that were used for creating the material from beyond the limit of *in-vitro* age for production.. Extensive viral testing was performed as part of these studies (reviewed by Rona LeBlanc).

Testing of cells beyond limit of in vitro age.
In order to challenge the cells and the process beyond the limit of *in-vitro* age for production, it was decided to ----------. A pilot plant run (----------) was executed, where the age of the cells that were expanded was as follows:
The number of generations was increased up to --- generations before the cells were seeded into the production reactor. This represents an increase in cell age of ---% compared to the normal process limitation of --- generations. The main production reactor was operated for --- days. This represents an increase in cell age of 33% compared to the normal process duration of --- days. The results of characterization on these cells is shown above in Table I.C.8.

Stability of the Expression Construct in Cells beyond the limit of in-vitro age
Cells beyond limit of in vitro age were tested for ----------. The age of cells that were cultured in a ----L bioreactor at the Lilly pilot plant was extended by ---% relative to the typical age limitations specified for production runs, as described above.
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Studies were done by a contractor: ----------

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Process flow for Cell Growth and Harvest Processes

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Description of Cell Growth and Harvest Process

The process flow for scale-up from WCB ampule to production bioreactor, as well as processing of the perfusate, from harvest to viral inactivation, is described in this section. For a given batch, the entire process up to ---------- is carried out in ---------- closed fermentation suites: ---------- Each of the seven steps in this part of the process (as well as subsequent steps in the purification process) have both critical process parameters that must be met, as well as criteria for forward processing. Process streams which fail to meet Criteria for Forward Processing will not be reworked or reprocessed.

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Containment and Inactivation

Appropriate measures in design of equipment and procedures have been taken at each stage of the manufacturing procedure to contain biologically active material, based on facility design. Small volume microbiologically contaminated cell culture materials and excess cell culture materials are locally decontaminated with ---------- Biohazardous and general solid waste generated in production and technical services areas are double bagged in biohazard bags and transferred to a central disposal facility in the basement, All of the bioreactors are closed systems. Once a cell culture has been shown to be contaminated with foreign growth, it is isolated from all other systems and the contamination is identified and investigated. There is the possibility that the contamination

may not be known before material is forward-processed. If this occurs, the process intermediate will be quarantined until full investigation is completed.

Precautions Taken to Prevent Adventitious Agent Contamination

The fermentation suites operate as closed systems and are validated as such. Because operations in these suites are carried out in closed systems, operators may work and move between the suite, the non-product containing medium preparation room, and the glasswash/autoclave room without changing oversuits. Operators and all equipment are dedicated to the manufacture of rhAPC. The design of the production facility provides a separation between cell culture/harvest (pre-viral inactivation) and purification (post-viral inactivation). Equipment and operators are not shared between the areas.

The HVAC air handling system is designed to mitigate the possibility of contamination of facility areas from both viable and non-viable airborne particulates.
All air handling systems within the cell culture suite are dedicated to the manufacture of rhAPC.

A comprehensive environmental monitoring program exists for the production facility. This includes chemical and microbiological monitoring of the source water supply, clean steam, water for injection and deionized water systems, viable and non-viable particulate air monitoring of key productions areas in both static and dynamic conditions, and surface monitoring of surfaces and laminar flow cabinets. Alert and action limits and corrective actions are established for all types of environmental monitoring. Additionally, at specified steps during production, settle plates and finger dab monitoring are carried out.

Manufacturing areas are cleaned and disinfected on a regular schedule in order to minimize the potential for contamination. Disinfecting agents are chosen for their ability to prevent development of resistant organisms and have been validated against routine flora found in the facility.

Comparison Between Pilot Scale and Commercial Scale Bioreactor and Harvest/Recovery Processes

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In-Process Controls for Bioreactor and Recovery Steps

The in-process controls for the cell growth, harvest, and initial recovery are of two types: the control of critical process parameters during the process, and criteria for forward processing (specifications) for designated steps of the process. Critical process parameters are control elements that are linked either to the achievement of the purpose of the step or to the prevention of an event deleterious to downstream processing. A deviation from the critical process parameters will trigger an investigation which may or may not result in material being forward processed or recycled.

There is then a schematic for scale-up to bioreactor, bioreactor, product recovery, and purification. This is followed by forward processing criteria for --- steps going from culture thaw and expansion to viral inactivation prior to the first purification step ----------. Justifications for the tabulated forward processing acceptance criteria, as well as critical process parameters, are also provided.

Reviewer's comment: The in-process controls and acceptance criteria for continued processing appear to be adequate

In-Process Controls for Purification

The in-process controls for the purification of the drug substance are of two types: critical process parameters and criteria for forward processing (in-process specifications). Critical process parameters are control elements that are linked either to the achievement of the purpose of the step or to the prevention of an event deleterious to downstream processing. A deviation from the critical process parameters will trigger an investigation which may or may not result in material being forward processed or recycled. Process intermediates which fail to meet Criteria for Forward Processing will not be reworked or reprocessed. Ranges are generated from either laboratory or pilot scale studies as noted.

Of note is the ---------- column (first column), and --------- use for the ---------- and --- uses for the ----------
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Drug Substance Process Validation

The drug substance process validation has been successfully completed and resulting data reviewed. All consistency runs were performed in compliance with established cGMPs and with approved validation protocols. All excursions from the validation protocol, which includes the Criteria for Forward Processing (CFP) and Critical Process Parameters (CPP), were thoroughly investigated, as required by the validation protocol and determined to have no impact on the validity of the consistency runs. Reports are available at the -------- ----------, ----------,--------, facility.

As requested by the FDA, the formal process validation protocol for Drug Substance Manufacture was supplied by Lilly as part of Amendment 8 to the BLA.

Validation of Cell Growth and Harvest

This section covers Steps ---- of the process, ---------- ---------- ----------. Data is presented in this section that demonstrate that the commercial scale process is capable of performing within the ranges described for both critical process parameters and criteria for forward processing and is comparable to data generated at the pilot scale in preparation of clinical trial material

This section contains average values, standard deviations, and ranges for processes at both Lilly ----------) and -------- (-------) processes, with the number of processes contributing to the data set from each facility being dependent on the parameter being validated. There are always at least ------- processes from -------- in the data set for parameter.

This section is generally acceptable. However, it is not clear in the BLA submission whether the -------- processes described were from the ----------. For instance, there is reference to both reactor ------- and ------- at the -------- manufacturing facility, but the train is not specified . Also, for some tabulated averages and SDs, there is no mention of the Batches contributing to these statistics. At the FDA's request, these issues were clarified in responses contained in Amendment 8.

5. Drug Substance Stability

Overview

The Drug Substance stability program consists of stability studies ---------- ---------- (---------) and studies of samples kept ---------- The BLA contains data on --------- -------- Batches, with data extending to -- months for both --- ^{0}C and --- ^{0}C storage. There is also ---------- month stability data at –40 ^{0}C for three Batches from the ---------- (---------- month's stability data for --- ^{0}C storage of these ---------- batches.

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Batches ------ and ------ are consistency batches.

The drug substance stability program consists of the following assays and time points. The specified assays were performed on all ------ -------- batches, as well as the ---------- development batches from ----------. As noted above, the BLA contains 9 months' stability data at ----^{0}C and ----^{0}C for the ---------- batches, and 18 months' data at ----- ^{0}C for the three ---------- batches, and --- months' data at -----^{0}C for these batches.

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For the development Batches, data is also presented for ----------). *Data was not shown for* ---------- After the stability program was begun for the development lots, the extinction coefficient for aPC was revised upward from ----------r mg/ml to ---------- mg/ml. This change caused an apparent ---------- for these lots during the stability program

Description of the storage vessels used for Drug Substance stability studies

Drug substance from each lot was stored in ---------- containers that duplicate on a reduced scale the container closure system (storage vessel) for the drug substance. The containers are cleaned with ----------, rinsed with ----------, then ---------- before adding drug substance solution. Drug substance solution sampled directly from the commercial drug substance storage vessel is placed into the stability container. The container is capped with a ----------. The drug substance solution is ---------- before being placed in an appropriate --------- for storage.

During the preapproval inspection of the -------- production facility, there was discussion of the fact that Drug Substance stability samples are initially ---------- at ---- ^{0}C, rather than -------- only to --- ^{0}C as is the case for the ----- liter ---------- used in actual production. This discrepancy was cited as a 483 item. In Lilly's June 29, 2001 response to the 483, Lilly agreed to amend the stability protocol to eliminate the ---------- at --- °C, instead placing the Drug Substance stability vessels in a ---------- immediately after they have been filled with aPC and sealed. In this response, Lilly included --- months of data to support --- ^{0}C stability for ------ lots of aPC (----------) in ---- liter production ----------, including ---------- as occurs in production. Lily noted that each of the Drug Product lots were used to product --- drug product validation lots, and therefore were subjected to ----------

Lilly's change in the Drug Substance ---------- method was deemed adequate.

An anomaly observed with Batch ---------- in the Drug Substance stability program.

Starting at the zero time point, low values were observed for ---------- for Batch ----- at both --- ^{0}C and --- ^{0}C, in the range of ---%, versus a range of ------- % for the other lots. These values were still within the lot release specification of ------%. This Batch was of concern because it was manufactured during the clean steam conductivity excursion at --------, which has received extensive review and discussion. This excursion was judged to have no detectable product impact (See Questions and Requests for the Manufacturer at the end of this review)

Summary of results from the Stability Program for -------- --- ml vessels

With the exception of the anomaly noted above, the rhaPC drug substance shows little or no change for as long as --- months in the --- ml -------- vessel stability program, either at the typical storage temperature of --- ^{0}C or ----------. The ---------- properties used to determine the stability of rhAPC drug substance were ---------- ----------. These properties are ---------- that can occur in solution. In addition, ----------, were used as stability indicators. The following table summarizes the ---------- results.

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The pooled slope is ---- Units/mg per month, which is not statistically different from ----------.

Stability of Drug Substance in the Storage Vessel

In addition to the primary stability program using storage in representative ----ml containers, the stability of rhAPC Drug Substance was investigated in a ----L pilot scale storage vessel which is commercial -----L storage vessel except for its reduced size. The contents of the pilot vessel containing rhAPC Lot ---------- were ---------- after --- and --- months of storage in a --------- maintained at ----°C. Samples were taken from the vessel and testing was performed. The results were compared to the initial test results for the lot. No significant degradation was evident over the --- month storage period. These data confirm that the stability results obtained from testing the Drug Substance stored in the ----ml containers are representative of the results obtained from testing the material stored in the large-scale drug substance storage vessel. These data also demonstrate that rhAPC Drug Substance is stable for at least --- months when stored at ----°C.

Moreover, as cited above in discussion of ---------- the --- ml storage, vessels, Lilly's June 29, 2001 response to the 483 Lilly included data to support ----- ^{0}C stability for two lots of aPC (----------) in ------ liter production ----------, including two ---------- as occurs in production----------. The second cycle used to dispense aPC for Drug Product occurred approximately --- months after the first, and thus this data in effect constitutes --- month stability data in the ---- liter production storage vessels. As shown tin the following table, there was no significant change in stability-indicating parameters during this --- month period.

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Stability of rhAPC Drug Substance After ---------- in the Commercial Storage Vessel

Because the Drug Substance may be thawed and re---------- ---------- lots of Drug Product, the stability of rhAPC Drug Substance was investigated throughout multiple ---------- in the ----- liter commercial storage vessel. The contents of the vessel containing a development batch of rhAPC, Lot ----------, were --------- and initial test samples were removed. The Drug Substance was ---------- ---------- for sampling, completing the first ----------. This ---------- process was repeated for a total of ----------. The drug substance was held at --°C for a cumulative time of --- hours. As is seen in the following two tables, ---------- ---------- produced no significant change in stability-indicating parameters.

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Planns for future stability testing

The frequency of stability testing for routine lots of rhAPC drug substance is at least ---------- per year. Samples will be stored in a small-scale equivalent of the commercial storage container. If a manufacturing change or deviation occurs and it is deemed necessary, additional stability testing will be undertaken.

Evaluation of rhAPC Drug Substance Stability in Solution

In order to determine which assays are most useful as indicators of stability, a development lot of rhAPC drug substance (Lot ----------) was stressed in solution at a range of pH values and temperatures, and analyzed using a variety of methodologies.. Solution stability was evaluated at ---------- The effect of

---------- on solution stability was evaluated at ----------

------) was substantially less than the level present in commercial rhAPC drug substance. Increased ---------- tends to ----------
---- of rhAPC, so the degradation rates observed in this study are greater than would be expected for rhAPC drug substance.

This study demonstrated that ---------- is the predominant degradation pathway for rhAPC in solution at ---------- Formation of ----------
---------- is much more rapid at --------- than at ----------, accounting for a more pronounced decrease in ----------, substantial rhAPC ----------
-- is observed by ----------, and this degradation pathway is most likely responsible for an extreme loss of ---------- at observed ----------
-- analysis did not reveal any additional degradation pathways. Based on these results, ---------
---------- appear to be the most useful stability-indicating assays for rhAPC.

Effect of added ----------on aPC in solution

The effect of added ---------- was evaluated using the same starting solution as described in the previous section. The adjusted solution contained ---------% ----------. This solution was stored at --°C and samples were removed for testing at ---------- hours. As seen in the following table, no significant degradation was observed in any of the assays following ---------- exposure, and, within assay variability, ---------- was unaffected

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---------- did not reveal any significant ---------- modifications for the sample after exposure ----------. However, upon addition of ---------- directly to the ----------, a number of the ----------, with a corresponding appearance of other ----------
----------. These data demonstrate that the ---------- assay will detect rhAPC ----------. However, ---------- does not appear to be a significant degradation pathway for rhAPC.

Conclusions Regarding the Drug Substance stability program

Lilly has presented a well-conceived program for examining the stability of -------- Drug Substance. This program is supported by ancillary studies to determine the most effective stability-indicating parameters, as well as studies on stability in --- and ---- L (production scale) vessels, studies on stability in solution, and studies on the effect of added ----------

The aPC Drug Substance appears to be stable for at least --- months when stored ---------- at ---°C and for at least --- months when stored -------- at ---°C. In Amendment 20 to the BLA, . If this data is satisfactory, it would probably be sufficient to support a --- month lifetime at ---^{0}C or an --- month lifetime at --- ^{0}C. However, based on equipment design of their ----------, Lilly is asking for a ---- month lifetime at –----- ^{0}C. This would seem to require continuing the --- ^{0}C stability program out to --- months.

Reviewer's comments

1. Because at the time of BLA submission Lilly only had real-time Drug Substance stability data for --- months at --- ^{0}C and --- or more months at --- ^{0}C, at approval the FDA can only grant an --- month lifetime at --- ^{0}C, with a post-approval commitment to extend the lifetime when data becomes available. ---------n month stability data at ---^{0}C was supplied in BLA Amendment 20. In response to Question 4 in the CM & C Discipline Review letter issued September 21, 2001, in Amendment 24 to the BLA Lilly clarified the --- ^{0}C specification for the Drug Substance storage --------- (See Questions and Requests for the Manufacturer at the end o f this review for further discussion.)

2. It is of concern that Batch ------- was made at the end of ---------- ----------resulting from ---------- ---------- (-------- 483 item #1)
However, this ---------- was judged to have no detectable product impact (See Questions and Requests for the Manufacturer at the end of this review for further discussion.)

6. Drug Product Manufacturing

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Components of Commercial 5 mg and 20 mg rhAPC Drug Product

The rhAPC Drug Product Solution prior to lyophiization nominally consists of 5 mg/ml rhAPC, ----------) sodium chloride, ----------) citrate and ---------- sucrose (solid-state stabilizer/bulking agent) Excipients as per Pharma European and USP-citrate formulation

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rhAPC Drug Product, 5 mg and 20 mg, will be supplied in a ---------- vial with a ---------- stopper that is secured by an ---------- crimp seal with a ---------- flip top. Prior to use, the drug product is reconstituted with an appropriate volume of sterile water for injection to a concentration of approximately 2 mg rhAPC per ml. The solution of reconstituted drug product should not be held longer than 3 hours in the vial, because it does not contain an antimicrobial preservative (i.e., non-preserved). The solution of reconstituted drug product must be further diluted with an appropriate volume of sterile 0.9% sodium chloride injection prior to continuous intravenous administration for up to --- hours.

A vial of the proposed commercial rhAPC Drug Product, 5 mg will typically contain a ---% excess (----- mg rhAPC/vial) and a vial of the proposed commercial rhAPC Drug Product, 20 mg will typically contain a --------% excess (-------- mg rhAPC/vial) to allow for delivery of the label claim.

The intended commercial batch sizes are ------- vials for the 5 mg presentation and -------- vials for the 20 mg presentation. Tables of ingredients and amounts.

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<u>Lyophilization</u>

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A study was conducted to evaluate the ---------- stability of solutions of reconstituted rhAPC Drug Product ---------- for --- hours. There was no significant change in ----------. However, although the reconstituted rhAPC Drug Product exhibits acceptable ---------- and ----------stability for up to ---------- the solution of the reconstituted drug product should not be held longer than 3 hours in the vial, because it does not contain an antimicrobial preservative.

A study was conducted to assess the in-use stability of I.V. solutions of diluted rhAPC Drug Product with readily available and commonly used I.V. bags and I.V. administration sets made of ----------

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A ---------- loss in rhAPC ---------- was observed during the first hour of pumping (delivery). ---------- does not significantly impact the delivery of
the drug. After the first hour of pumping, no further ----------is evident, because the rhAPC ---------- of the pumped samples from later time points were the same as that of the initial (0 hour) sample. No significant change (within assay variability) was observed in the ---------- stability, as indicated by the ---------results, during this in-use stability study. The results of this in-use stability study support continuous I.V. administration of the proposed commercial rhAPC Drug Product for up to --- hours at commonly-used infusion rates of 5 ml/hr to --- ml /hr with the rhAPC concentration in the I.V. solution ranging from 100 µg/ml to 200 µg/ml.

Compatability with ---------- bottles and --- syringes was also demonstrated (reviewed but not shown).

Reviewer's comment.
Lilly has advised the FDA , via submission of Amendment 13 to the BLA, as well as via teleconference July 31, 2001, that more extensive studies on stability upon dilution into IV solution support 12 hour stability, but indicate an unacceptable loss of activity at --- hours. Therefore, in the Package Insert Lilly has to shortened the recommended lifetime upon dilution to 12 hours. Data from Amendment 13 supporting this change are summarized below in Table 4 from Amendment 13.
Dilutions of rhaPC from five different Drug Product lots were used in this study:
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In order to assess the effect of different IV bag plastic formulation, rhaPC was diluted into three different types of normal saline IV bags; i.e.
Saline solution A : ----------, Saline solution B : ----------
Ssaline solution C: ----------
[

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In these studies, the ---------- for the diluted rhaPC solution observed after --- hours showed declines in the range ---------- while declines at --- hours showed a range of ----------). Based on this data, the change in recommended lifetime in an IV bag appears to be a justified in terms of reducing variability and overall loss of activity.

Certification of Excipients

The excipients used in manufacture the rhAPC Drug Product 5 mg and 20 mg presentations comply with the monographs of both the Ph.Eur. and the USP/NF. Sample ------

------- Certificates of Analysis are provided for the excipients; i.e----------
---
----------. These COAs contain the batch number, date when qualification tests were passed, and manufacturing release date. These specifications for excipients appear adequate. The endotoxin specification for Water for Injection is ----------.

Name and Address of the Manufacturers for rhaPC Drug Product

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5. Lot release testing of the rhAPC drug product for ----------
---------- will be performed at:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285-0002
USA

[

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7. Final Quality Control release of the rhAPC packaged drug product will be performed by:
Eli Lilly and Company
Lilly Technology Center
Indianapolis, Indiana 46285-0002
USA

8. Stability testing of the rhAPC drug product will be performed at:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285-0002
USA
and
Eli Lilly and Company
Lilly Technology Center
Indianapolis, Indiana 46285-0002
USA

Other Products
Other products manufactured at ----------. are provided in Drug Master File No. ----------

Description of the Manufacturing Process. 89

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Formulation

-------- rhAPC Drug Substance is ---------- and ---------- in, (---------- to produce homogenous rhAPC Drug Substance Solution. A calculated quantity of rhAPC Drug Substance Solution is then transferred to a suitable, temperature-controlled, primary compounding vessel to produce rhAPC Solution Section. ---- lots of

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the procedure as described above. The action limit from the start of the transfer of the rhAPC Drug Substance Solution into the primary compounding vessel (defined ----------) to completion of the sterile filtration is --- hours.

Reviewer's comments

1. *What is the process for deciding whether or not to* ----------
2. *Similarly, how is a decision made to* ----------

These questions were discussed during the ---------- inspection, and resolved in Amendment 20 to the BLA (See Questions and Requests to the Manufacturer at the end of this review, # 5 and # 6)

Container Closure

---------- 5 ml and/or 20 ml vials are cleaned using validated washing cycles in an automated vial washing machine. The vials are ---------- sterilized and depyrogenated by ---------- The vial closures (i.e., 13 mm and 20 mm ---------- stoppers for 5 ml and 20 ml vials, respectively) are washed and ---------- sterilized using validated washing and sterilization cycles in an automated stopper washing/sterilization machine. Validated washing cycles are designed to provide a ----------

Filling

Filling equipment that has been sterilized by ---------- is used for filling the sterile solution into vials.. The sterile-filtered rhAPC Drug Product Solution is subjected to an ---------- vessel containing Drug Product Solution and the filling equipment. ----------. The sterile-filtered solution is aseptically filled into sterile vials and sterile stoppers are partially inserted into the vials. Filling checks are conducted during the filling operation at regular intervals and are compared to the theoretical filling weight. The same rhAPC Drug Product Solution is used to produce both the 5 mg and 20 mg presentations by varying the amount of sterile-filtered solution filled into appropriate size vials.

Reviewer's comment

Is there mixing of the Drug Product solution after ---------- immediately before filling? ----------. *This issue was discussed and resolved during the ---------- inspection (See Questions and Requests to the Manufacturer at the end of this review, # 8).*

Lyophilization

The filled vials, with partially-seated stoppers, are loaded into a pharmaceutical-type freeze dryer for lyophilization. The filled vials are processed under conditions that result in the product being -------- --------C before primary drying is initiated. Shelf temperature and chamber pressure (vacuum level) are controlled and monitored throughout the freeze-drying process. Predetermined primary-drying and secondary-drying hold times at the established temperature/pressure conditions prevent product collapse and result in a drug product with low moisture (water) levels. The freeze-dryer chamber pressure is then ---------- ---------- and the stoppers are then fully seated into the vials.

Capping and Sorting

The vials are removed from the freeze dryer and passed through a capping machine for application of an ---------- seal. After sealing, all vials are inspected for visible defects and unacceptable units are discarded. Random samples are removed for assay for release specifications----------.

Repeat Operations

If necessary, normal operations described within the batch record, such as ---------- ---------- as needed in accordance with current Good Manufacturing Practices. The option for ---------- is discussed at the end of this review under Questions and Requests for the Manufacturer, # 7.

Labeling and Secondary Packaging

Nude vials are transferred from the manufacturing area to the packaging area for labeling and secondary packaging. Labels are affixed to the vials and the labeled vials are subsequently packaged into the appropriate secondary packaging.

Reviewer's comment

Does ---------- make other lyophilized products in the same, or similar vials? What precautions are taken to prevent the nude (unlabelled) rhaPC vials from getting mixed up with unlabelled vials for other products? This was discussed and resolved during the ---------- inspection (See Questions and Requests for the Manufacturer at the end of this review, # 9)

Sampling Plan

Samples are removed at various intervals based upon the assay to be performed, according to the following table. In-process samples are taken as indicated in the table below. Dose checks are performed at regular intervals. Samples of the drug product for release testing are removed randomly from the lot.

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As per my request, the formal Process Validation Protocol used to validate Drug Product process was submitted in Amendment 8 to the BLA. The Process Validation Protocol from ----------. is dated October 10, 2000, with final sign off on October 9, 2000 from four Lilly representatives. This precedes the manufacture of validation lots, as the first 5 mg Drug Product Validation Lot (---------) was executed October 13, 2000, and the first 20 mg Drug Product Validation Batch (----------) was executed October 18, 2000. The Process Validation Protocol specifies manufacture of ------ 5 mg validation lots, and -------- 20 mg validation lots. The protocol contains detailed specification of the Drug Product manufacturing process, Critical Product parameters, and requisite analyses. Sampling procedures and the process for validation of lyophilization is spelled out in considerable detail. The Drug Product Process Validation Protocol is adequate.

In-Process Controls

As shown in the following table, there are --- steps in the Drug Product process, and --- parameters are briefly described, with their specified limits.

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Release samples are pulled ----------, with the exception of samples for ---------- which are pulled at the ----------
and end of the batch.

Specifications and Methods for Drug Product

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Reviewer's comments on Lot release specifications for the Drug Product

1. In Amendment 13 to the BLA, Lilly increased the lower limit for potency from 300 U/mg to 350 U/mg. In the same amendment, Lilly reduced the recommended lifetime for rhaPC diluted in IV solution from 24 hours to 12 hours Both changes are aimed at providing higher and more consistent activity during patent infusion.

2. As per FDA request, ---------- has developed and validated a new ---------- assay for the Drug Product, and has lowered the ---------- specification from ---------- rhaPC to ----------rhaPC. This information was submitted in BLA Amendments 8 and 11, and represents a validated improvement in product specification. The Drug Product ---------- specification is now satisfactory.

3. In the Specifications from the BLA, ---------- is the only identity test for Drug Product. Lilly has since agreed via Amendment 24 to make Phase IV commitments for two additional identity tests: a)The ---------- assay will be validated and used for identiy and purity b) ---------- analysis will be validated as an assay for identity.

4. As part of the Lily response to an Indianapolis PAI 483 citation, Lilly has agreed to lower the ---------- specification.

5. [

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Certificates of Analysis for Validation Lots

The BLA Certificates of Analysis for the ---------- validation lots of the 5mg presentation, and COAs for ------ 20 mg presentations.
As specified in the Process Validation Protocol, these lots of the drug product have been produced at full scale by the commercial process in the commercial facility, ----------. These lots were manufactured in October and November of 2000.

Analytical Data for rhAPC DrugProduct Lots

Throughout the drug development process, the analytical methodologies and specifications for rhAPC Drug Product have evolved. Although the technologies used for

these methods (e.g. ----------.) have not changed, the tests have been enhanced for greater selectivity and
reproducibility. Therefore, only recent lots of material have been analyzed by the current revisions of the analytical methods provided in this submission. The reporting limits for some of the earlier analytical methods also may be different from those listed under the current methodology.

Data has been supplied for the --------- ----------5 mg validation lots:---------- ---------- and the -------- 20 mg validation lots from Catalytica: ----------This data is shown in the following tables:

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Also presented is batch analysis for 10 mg clinical lots produced using the commercial process, as well batch analysis for 10 mg clinical lots produced using the -------- process (for Phase I and II). It is of note that analyses of all the clinical Drug Product lots were more extensive than the analyses used for the commercial lots. The clinical lots were routinely characterized for ----------. In addition, the Drug Product made from the -------- material was characterized for ---------- Furthermore, and perhaps most importantly, the ---------- Drug Product was analyzed for ----------, as well as content of specific ----------

Reviewer's comments

It is my opinion, with the agreement of Gibbes Johnson, that Lilly , as a Phase IV commitment, should institute ---------- as part of the Drug Product stability program, and possibly as a lot release for the Drug Product. This issue has been addressed in amendment 24 to the BLA, and is discussed in the Questions and Requests to the Manufacturer section at the end of this review, # 10.

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Analytical Methods and Validations for rhAPC Drug Product

The analytical methods that are used to control both drug product and drug substance are : identity and purity of aPC (----------, ---------- For these assays common to Drug Substance and Drug Product, ----------, ---------- are performed at ----------, while ----------, and ---------- are performed at Lilly Assay for water content, which is done only for Drug Product, is performed at Lilly. These methods were reviewed by Gibbes Johnson during PAI inspection August 7-8, 2001. Lot release tests for Drug Product that are performed at ----------are: ----------

Reviews of the ---------- method of water determination, ---------- and the properties of reconstituted solution method are found at the end of this document.

Container Closure System for rhAPC Drug Product

The commercial rhAPC Drug Product is a lyophilized (freeze-dried) powder in a glass vial for parenteral use and will be commercially available as both 5 mg and 20 mg presentations. Prior to lyophilization, an appropriate amount of rhAPC Drug Product solution is filled into appropriate size -------- glass vials, which have been treated with ----------. Both presentations of lyophilized drug product use an appropriate size ---------- stopper. The product contact portion of the stopper has a ----------, which is inert and does not interact with the drug product. A ---------- is applied to the non-product contact surface to ---------- stopper to facilitate handling

during the seating and stoppering operations. The ---------- and forms ---------- surface, eliminating ---------- particulates from the stopper. ---------- seals with flip caps will used to secure the stoppers in place.

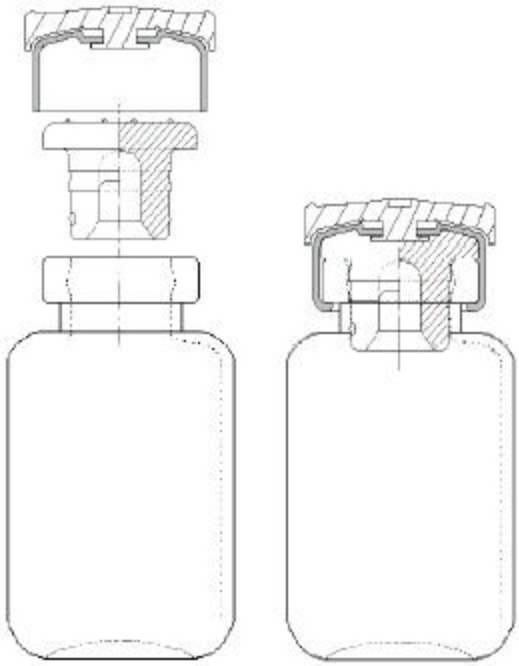

Figure II.F.1. Assembled Container Closure System

Suitability of the container components

The elastomeric components meet the requirements of the USP <381>, Elastomeric Closures for Injections. The glass meets the requirements of the USP <661>, Containers: Chemical Resistance - Glass Containers.

Because the reconstituted rhAPC drug product is aqueous with a nominal pH of ---, the extraction properties of the solution of reconstituted drug product are not reasonably expected to be different from that of water. Therefore, extraction testing of the elastomeric closure does not need to be repeated with the drug product. Manufacturer's extractable data, contained in ---------- provides assurance that the elastomeric closure is safe for use with the drug product.

Sterilization Process Validation

As technological changes occur and additional data are analyzed, Eli Lilly and Company or ----------. may change their validation practices in accordance with corporate change control policies. Consequently, the information and data supplied in this document do not require revision during annual updates to the Food and Drug Administration.

Reviewer's note

Lilly needed to clarify whether or not this is a general policy statement, versus the statement "the information and data supplied in this document do not require revision during annual updates to the Food and Drug Administration" referring specifically to sterilization validation. This issue was discussed during the ----------inspection, and resolved in Amendment 20 to the BLA. For further discussion, see the Questions and Requests to the Manufacturer section at the end of this review, # 12.

Overall Manufacturing Operation.
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Reviewer's comment
In May, 2001 Lilly notified the FDA about an excursion in the function of the ---------- ---------- equipment used in sterilization of the Drug Product vials, in which the ---------- ----------. This has necessitated re-validating the ----------, and production of further Drug Product consistency lots after this validation. Data on was submitted to the BLA as Amendment 1., and the issue was addresses during the ----------PAI and in further discussions between Laurie Norwood, Lead Inspector, and ----------.

Schematic of Overall Drug Product Manufacturing
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Drug Product Solution Filtration

The Customized Buffer Solution and rhAPC Drug Product Solution are compounded as described in the manufacturing process (batch formula reference). In-process samples for ---------- are collected from the rhAPC Drug Product Solution during the compounding process. The Customized Buffer Solution is filtered through a -------- µm filter as it is added to the rhAPC Drug Substance Solution. Although this filter may be sterilized prior to use, the purpose of this filter is ----------. The specification for pre-filtration ---------- is no more than ---------- . The tank containing the rhAPC Drug Product Solution is pressurized with ---------- to transfer the product to a sterile holding tank through a pre-sterilized --------µm filter. ---------- testing is performed before and after
filtration of the solution.

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Specifications Concerning Holding Periods

Time limits for specific phases of production have been established to ensure microbiological, chemical, and physical purity of the product. These time

limits include:
•--- hours from the start of rhAPC Drug Substance Solution dispensing to the completion of sterile filtration;
•--- hours from the preparation of the Customized Buffer Solution to transfer to the tank containing rhAPC Drug Substance Solution; and
•--- hours from the end of filtration to the start of the freeze dryer cycle.
Time limits were established based on product development data, ---------- and ---------- studies. In --- hours, there is no significant ---------- in the Drug Product buffer

7. Drug Product Stability

Drug Product stability assessment is performed at Lilly manufacturing facility in Indianapolis The stability of rhAPC drug product is demonstrated by --- primary stability lots and --- supporting stability lots. The test results for --- additional clinical lots and --- development batch are also included as additional evidence of rhAPC Drug Product stability. ----- of the primary stability lots are the commercial 5 mg presentation, and the other three primary stability lots are the commercial 20 mg presentation. All -----supporting stability lots are the 10 mg presentation. The additional ------ lots are also the 10 mg presentation. The process for setting specifications and determining the recommended shelf life utilized the stability information from both the primary and supporting stability studies. This approach was justified by performing ----------tests to demonstrate that the stability profiles were similar for all --- lots over all ----- product presentations. Currently, 18 months of data are available for the primary stability lots, and --- months of data are available for the supporting stability lots.

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Drug Product Stability Protocol

The analytical properties used to determine the stability of rhAPC Drug Product are----------(Protein C: Activated), ---------- which are indicative of ---------- which can occur in solution, and potentially in the lyophilized state. The ---------- test will detect ---------- that can occur in the lyophilized state. The -------- test (Protein C: Activated) will detect any ---------- regardless of the cause. The ----------of the drug product is measured to demonstrate that the amount of----------remains acceptable throughout the storage period. The above parameters are also investigated after reconstitution and holding for up to --hours to determine the stability of the rhAPC drug product formulation in the solution state.

---------- are additional parameters tested on the lyophilized drug product to ensure ---------- into the container is minimal and does not affect the formulation.

---------- is performed to ensure the integrity of the container closure system for prevention of ---------- throughout the defined dating period.

---------- is performed to ensure acceptable ---------- throughout the storage period.
In addition to the proven stability-indicating tests, the protocols contain tests for ----------
----
The
tests for ---------- were performed for the primary stability batches only.

The analytical properties used to determine the stability of rhAPC Drug Product are ----------
---------- (Protein C: Activated----------
----------which are indicative of ---------- of the molecule which can occur in solution, and potentially in the lyophilized state.

The above parameters were also measured after reconstitution. At various time points throughout the studies, the stability of rhAPC Drug Product is determined after reconstitution. Samples of lots placed on stability are pulled at the ---------- month time points. The contents of the vials are reconstituted with Sterile Water for Irrigation (Injection) and held at ---------- The results of these samples are compared to a sample reconstituted and analyzed immediately (0-hour).

Graphs of the measured stability indicating parameters show no appreciable change, even under accelerated conditions (---------- relative humidity for up to -- months)
Shown are below are graphs of activity at normal and accelerated conditions

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The pooled slope ---------- per month, which is not statistically different from zero.

Also shown below is the pooled graph for ----------, as determined by the ---------- method. Note that the slope remains $\leq$ 1% water content, even though lot release specification is set at --%. The Drug Product manufacturing history given in the BLA, extending from lots made with the -------- process all the way through commercial lots shows water content ---%, indicating that -- % lot release specification is excessively liberal.

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Reviewer's comments
1. Is the request for -- month stability justified on the basis of the 10 mg -- month stability data? This issue was addressed in Amendment 24 to the BLA (see Questions and Requests to the Manufacturer at the end of this review, # 13)
2. As discussed elsewhere, Lily should make a Phase IV commitment to add ---------- analysis to the stability program. This issue was addressed in Amendment 24 (see Questions and Requests to the Mnaufacturer at the end of this review, # 10).
3. Stability data on ----------, taken together with the Drug Product manufacturing history, indicates that the ---------- never exceeds the --% range, and that the --% lot release specification should be lowered. This issue was addressed in responses to the Lilly---------- PAI.

Photostability

--- rhAPC primary stability lots, ----------(5 mg presentation) and ----------(20 mg presentation), were used to determine the effects of exposing unlabeled and packaged vials of product to visible and UV light. These lots are representative of the commercial formulation and were in the commercial vials with and without the commercial boxes described. As per the ICH guidelines on photostability testing of new drug substances and products, the light source described in option 1 ----------) was used for exposing product. Samples were exposed to an overall illumination of ----------

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lyophilized drug product. There was no change for ----------, even for ----- vials. There was also no change in ---------- for the 20 mg ----- vials, while there was a ----% decrease in ---------- for the 5 mg vials

Reviewer's comment
There was no change in ---------- content or ---------- for packaged vials, indicating the normal conditions for storage, which would be in cardboard boxes, is adequate.
The package insert reads as follows:

Preparation and administration instructions: Use aseptic technique.

…….

10. Avoid exposing Xigris solutions to heat and/or direct sunlight. No incompatibilities have been observed between Xigris and glass infusion bottles or infusion bags and syringes made of polyvinylchloride, polyethylene, polypropylene, or polyolefin.

(and)

How Supplied

…….

Xigris should be stored in a refrigerator 2° to 8°C (36° to 46°F). Do not freeze. Protect unreconstituted vials of Xigris from light. Retain in carton until time of use. Do not use beyond the expiration date stamped on the vial.

Plans for future stability studies

Three production lots of rhAPC Drug Product will be placed on stability using the following protocols.

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In Amendment 24 to the BLA, Lilly has committed to placing at least one lot of the 5 mg presentation and at least one lot for the 20 mg presentation on stability each year. If a manufacturing change or deviation occurs and it is deemed necessary, additional stability testing will be undertaken. The protocol is as follows:

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The stability data will be reported in the annual report. Lilly will continue to monitor the drug product for potential changes in degradation products. If a change or deviation occurs and it is deemed necessary, additional stability testing will be undertaken. Based on sound scientific principles and after proper review and approval, time points and/or tests may be added to the stability protocol. Should any lot of rhAPC drug product fail to meet product specifications during the approved dating period, Lilly will withdraw the lot and a thorough investigation will follow any product withdrawal.

Conclusions: Recommended Expiration Dating and Storage Conditions

The analysis of the stability data demonstrates that a --- month shelf-life can be assigned to rhAPC drug product when stored at 2 ^{0}C to 8 .^{0}C (46 ^{0}F to 59 ^{0}F). The lyophilized drug product may be exposed to temperature and relative humidity conditions up to ---^{0}C and ---%

relative humidity (e.g. during shipment of product) for up to -- months. Chemical and physical stability of rhAPC Drug Product has been demonstrated for -- hours at ---^{0}C after reconstitution. From a microbiological point of view, the product should be used immediately after reconstitution. If the product is not used immediately, it may be held at room temperature (15 ^{0}C to 30 ^{0}C [59 ^{0}F to 86 ^{0}F]), but must be used within 3 hours

8. Drug product Methods

The following section contains reviews of methods and method validations used for Drug Product; i.e. determination of water content, osmolarity of ---------- and solution characteristics of reconstituted product.

1. Method B07016

Determination of water in recombinant rhaPC Drug Product by ----------

Summary

Method B07016 was developed for the determination of water in Recombinant human activated Protein C (rhAPC) by ----------. This method meets the requirements of the USP general test <921> for water determination. Coulometric measurements are performed using a ---------- instrument, or equivalent. [

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1. ----------and ---------- solution used in cell banks

Specifications are provided for the ----------, and ---------- solution. These media are not routinely tested. -------- should commit to testing ---------- medium, -------- medium, and the ---------- solution.

A request for this commitment was conveyed 8f of the CM & C Discipline Review letter issued September 21, 2001. Lilly provided a satisfactory response to this request in Amendment 24 to the BLA; i.e.

Question 8f

Please implement routine testing of the ---------- media, and the ----------Solution for ---------- and other parameters as appropriate. Please provide specifications for this testing.

Lilly Response

The specifications for the----------media are:

[

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----------Solution used in cell banking is made up at the time of use by combining ----------
----
are controlled according to the specifications provided in the initial BLA, Section I.C.1.a.1., Specifications and Test for Purchased Raw Materials. Based on the specifications for the----------media, the ---------- and ----------
provided in the BLA, Eli Lilly and Company believes that the ----------Solution is adequately controlled based on its preparation as required.

I agree that the preparation and content of ---------- solution appears to be adequately controlled.

2. <u>Manufacturers of ------ and ----- media</u>

Lilly must specify the manufacturers of ------ and ----- media.

A request for this information was conveyed to Lilly in Question 7 of CM & C Discipline Review letter from September 21, 2001. Lilly provided the requested information in Amendment 24 to the BLA; i.e.

> **Question 7**
> ***Please specify the manufacturers of the ------ and ----- media used in cell banking, and supply Certificates of Analysis for these media.***
>
> **Lilly Response**
> "The raw materials ------ and -----, used in Cell Culture and Harvesting, Step Nos. 3 (----------) and 4 (----------) are supplied by both ----------
> ---------- The Certificates of Analysis for the ------ (----------
> medium)
> and ----- (-------- powder) from both suppliers are provided (on the following pages-reviewed but not shown in this discussion).

This description of the manufacturers is adequate

3. Drug Substance Stability to be granted at approval

Because at the time of BLA submission Lilly only had real-time Drug Substance stability data for --- months at ---^{0}C and --- or more months at --- ^{0}C, at approval the FDA can only grant an ---month lifetime at --- ^{0}C, with a post-approval commitment to extend the lifetime when data becomes available. ---------- month stability data at ---^{0}C was supplied in BLA Amendment 20.

In response to Question 4 in the CM & C Discipline Review letter issued September 21, 2001, in Amendment 24 to the BLA Lilly clarified the --- ^{0}C specification for the Drug Substance storage ---------; i.e.

> **Question 4**
> ***The BLA contained drug substance stability data for up to -- months at --- °C and -- months at --- °C. Based on these data, an expiration dating period of -- months at --- °C can be granted. Please provide a stability protocol for FDA review. Upon review and approval of this protocol, data supporting extension of the dating period can be submitted in an annual report.***

Lilly Response

Storage of recombinant human Activated Protein C drug substance at -------- ----------. is in a --------- with a setpoint of ---°C with a tolerance of approximately -------°C. While the storage temperature for the drug substance is described in the initial BLA as "Less than or equal to ---°C," (Section I.G., Container Closure System), this represents a worst case scenario. In addition, ------- month stability data at accelerated storage conditions (---°C) provides assurance that the drug substance remains stable during possible brief excursions above the --------- setpoint of ---°C. Therefore, Eli Lilly and Company believes that the --- months long-term stability data (---°C setpoint with a tolerance of approximately --------5°C) for the primary drug substance lots submitted September 7, 2001, Serial No. ---, supports an expiration dating period for the drug substance of --- months. When --- month stability data is completed according to the stability protocol provided in Section I.H.1., Drug Substance Stability Protocol, page 799, Eli Lilly and Company will extend the expiry dating to --- months and submit the data in an annual report as required by 21 CFR 601.12(d)(2)(iii). In addition, at least one lot of drug substance will be placed on stability according to the Stability Protocol for Future Lots provided in Section I.H.1.a. Drug Substance Data, page 840.

Moreover, as noted above in the review of Drug Substance stability, the stability of rhAPC Drug Substance was investigated in a --- liter pilot scale storage vessel which is representative of the commercial ---- liter storage vessel. The contents of the pilot vessel were --------- after -

-- and --- months of storage in a --------- maintained at ---°C. These data demonstrated that rhAPC Drug Substance is stable for at least 18 months when stored at ---°C

It is the opinion of this reviewer and BLA Committee Chairman Gibbes Johnson that there is adequate justification for an --- month Drug Substance lifetime, and also an adequate proposal for extending the lifetime to --- months when data becomes available.

4. Anomalous Observation on Batch -------

Lilly should supply some rationale for the relatively low ---------- value for Batch -------. It is of concern that Batch ------- was made at the end of the Clean Steam conductivity excursion resulting from ---------- in the tap water used to supply the Clean Steam system (-------- 483 item #1)

This issue has been included in the consideration of the Clean Steam conductivity excursion, which has been the subject of extensive review and discussion between myself, BLA Committee Chairman Gibbes Johnson, and Lead Investigator Laurie Norwood. The ---------- value is still within lot release, and is not judged to be of concern. The impact of the clean steam excursion on this and other lots has also been judged to not be of concern, since the lot release data show and stability data show no product impact. A memorandum reviewing this data is attached.

5. ---------- of the Drug Product before Sterile Filtration

What is the process for deciding whether or not to ---------- the rhaPC Drug Product solution?

6. ----------the Drug Product during Filling

How is a decision made to -------- the Drug Product solution during filling?

Issues 5 and 6 were discussed during the ----------PAI. In ---------- of the drug product are never performed, and descriptions of these operations are not contained in the Batch Record. Therefore Lilly and ----------agreed to remove descriptions of these operations from the BLA. This agreement is found on page 1 of Amendment 20 to the BLA; i.e.

"In the BLA the Sterile Filtration, Section II.D.1.c., Description of the Manufacturing Process, has been amended to remove the following from the initial paragraph:
'The rhAPC Drug Product Solution ----------.'; and 'The sterile rhAPC Drug Product Solution ----------' This change has been made so that the BLA accurately reflects the drug product manufacturing process."

7. Drug Product ----------

The Drug Product manufacturing section of the BLA (page 90) contains a description of the sterile ---------- of drug product solution after a ---------- test. Lilly must submit to the BLA a validation study which supports this ---------- step and includes an analysis of drug product stability following such a ----------

This issue was communicated to Lilly via Question 5 of the CM & C Discipline Review letter issued September 21, 2001. Lilly responded in Amendment 24 to the BLA, by providing results of a validation study for ---------- using Development Batch ----------, which was manufactured at ----------; i.e..

Question 5

The drug product manufacturing section of the BLA (page 90) contains a description of the sterile ---------- of drug product solution after a ---------- test. Please submit to the BLA a validation study which supports this ---------- step and includes an analysis of drug product stability following such ----------

Lilly Response

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These analyses indicate no product impact of ----------.

In order to demonstrate that refiltration has no significant effect on stability, Lot ----------was analyzed after ----months of storage at ---------- conditions. ---------- storage was taken to represent a “worst-case” situation. Lot ---------- was stored at controlled----------conditions of -----°C for the first --- weeks and was then then transferred to an ---------- storage area. The temperature of the ---------- storage area is controlled at a setpoint of -----°C. The upper-alarm setpoint is ---°C and the lower-alarm setpoint is ---°C. The temperature typically ranges from ----------°C. Results of physico-chemical analyses conducted at the initial time and at --- months are shown in Table 2.

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9. Are Similar vials used at ----------

Does ----------make other lyophilized products in the same, or similar vials? What precautions are taken to prevent the nude (unlabelled) rhaPC vials from getting mixed up with unlabelled vials for other products?

This issue was discussed and resolved during the ----------PAI. There are no similar vials in use at ----------

10. ----------analysis for Lot Release of the Drug Product

There is no ---------- analysis for lot release. It is this reviewer's opinion that Lilly should commit to performing ---------- analysis. This Analysis was performed for the -------- product.

This issue was conveyed to Lilly via Question 8b of the CM & C Discipline Review letter issued September 21, 2001. Lilly responded in Amendment 24 to the BLA by demonstrating stability of both Drug Substance and Drug product ---------- patterns, and provided a commitment to develop ---------- analysis as part of Drug Product lot release; i.e.

Question 8b

Please perform analysis of drotrecogin alfa (activated) ----------, including ---------- content, in the drug substance and drug product stability studies to suppport the expiration dating. Please implement this analysis for use as a drug product release test.

Lilly Response

Data demonstrating ---------- stability has been obtained for both drug substance stored in the ----------at ---°C for --- months as well as drug product (Lot ----------) stored at --°C (from Drug Substance Lot ------) for --- months. ---------- was evaluated using the lot release ---------- assay. Full-scale drug substance Lot ----- was tested after having been stored for -- months at ---°C and subjected to a total of three ----------. Drug product lot CT15074 was tested after storage for -- months at --°C. Figure 1 shows the ---------- of rhAPC drug substance Lot ----------at initial and after storage for --- months at approximately ---°C. The comparative ratios (calculated as described in Method ----------) and calculated ---------- (a quantitative measure of the degree of ----------) are listed in Table 1. The comparative ratios and ---------- are comparable between the initial and -- months samples and compare favorably with that of the rhAPC reference standard --------. These results demonstrate that the rhAPC ---------- profile is stable throughout the storage period. Based on known properties of ---------- the most likely change in ---------- one might observe during storage would be a loss of ----------. A decrease in --------- content would be reflected in a relative increase in the earlier eluting peaks (e.g. ----------), a relative decrease in later ----------), and a corresponding reduction in the calculated ---------- No such changes were observed, thereby demonstrating that --------- is not lost from the rhAPC drug substance during storage nor during ---------- cycling.

Figure 2 shows the ---------- for rhAPC drug product Lot ---------- after storage at --°C for --- months. The comparative ratios and calculated "---------- are provided in Table 2. The data obtained for the drug substance lots used to produce drug product lot ----------) are also provided in Table 2 for
comparison purposes. These data demonstrate that the ---------- and ----------for rhAPC drug product stored for --- months at --°C are comparable to that of the rhAPC reference standard as well as typical rhAPC drug substance lots. Hence neither the drug product (fill finish) manufacturing process nor storage at --°C for --- months has a significant impact on the ---------- profile of rhAPC.
To provide further assurance that ---------- of rhAPC drug product remains consistent a ---------- test will be developed and implemented as a lot release assay by September 1, 2002.

To provide further assurance that ---------- of rhAPC drug product remains consistent a ---------- content test will be developed and implemented as a lot release assay by September 1, 2002.

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It is my opinion, in agreement with Gibbes Johnson, BLA Committee Chairman, that in addition to performing ---------- analysis for Drug Product lot release, Lilly should commit to using this analysis as part of the Drug Product stability program.

11. <u>Water content of the Drug Product</u>

The water content specification is set at--%, yet the manufacturing history appears to never show water content significantly greater that 1%. This specification should be revised to reflect manufacturing history. This issue has addressed as part of the response to the Indianapolis 483 report.

12. Sterilization Process Validation

It is stated "As technological changes occur and additional data are analyzed, Eli Lilly and Company or ----------. may change their validation practices in accordance with corporate change control policies. Consequently, the information and data supplied in this document do not require revision during annual updates to the Food and Drug Administration." Lilly must clarify whether or not this is a general policy statement, versus a specific reference to sterilization validation. Even in this specific context, this statement may not be acceptable to the FDA.

This issue was discussed during the ----------PAI, and Lilly agreed to remove this statement from the BLA. This change is contained on page 1 of Amendment 20 to the BLA, i.e.

In the BLA the Sterilization Process Validation (Section II.G.) contained the sentence "Consequently, the information and data supplied in this document do not require revision during annual updates to the Food and Drug Administration." (paragraph 3 of the Introduction, Section II.G.1.). This has been replaced with "Any changes to the sterilization process will be reported to the Food and Drug Administration as required by 21 CFR 601.12."

13. Stability to be granted for the Drug Product at Approval

Data for --- month stability on the 10 mg clinical formulation may not be adequate to support --- month stability for the commercial 5 mg and 20 mg formulations.

This statement was conveyed to Lilly via the CM & C Discipline Review letter issued September 21, 2001. Lilly responded satisfactorily on page 17 of Amendment 24 to the BLA; i.e.

Question 6

***Please note that --- month drug product stability data on the 10 mg clinical formulation is not adequate to support --- month expiration dating for the commercial 5 mg and 20 mg formulations. Additional real time stability data for the 5 mg and 20 mg formuations submitted in your September 7, 2001 amendment is sufficient to support an 18 month expiration date. Please submit a revised drug product stability protocol that provides for placing a least one lot of both the 5 mg and 20 mg presentations on stability each year. Upon review and approval of this protocol, data supporting extension of this dating period* can be submitted in the annual report.**

Lilly Response

"When --- month stability data is collected from the primary stability study, from the protocol provided in Section II.H.1., Drug Product Stability Protocol, page 233, the dating for the 5 and 20-mg drug product presentations will be extended to a shelf-life of

--- months. These data, supporting the dating extension, will be submitted in the annual report as required in 21 CFR 601.12(d)(2)(iii). In addition, at least one drug product lot of both the 5 and 20-mg presentations will be placed on stability according to the Stability Protocol for Representative Lots provided in Section II.H.2., Future Stability Protocol, page 342."

This response is satisfactory for granting 18 month stability at the time of approval.

14. Validation of the ---------- water determination method

a. The validation of accuracy for this method states that "Water was spiked into each of ---- dosage forms. The recovery ranged from ---------- of theory, with a mean recovery of -----%." Lilly should clarify how much water was spiked into these samples

b. The validation of range for this method only extends to -- % water. Lot release for Drug Product water is set at --%. Lilly should explain how this specification can be reconciled with an upper validation of ----% water for this method?

These issues related to water content in the Drug Product were discussed during the Indianapolis PAI, and was satisfactorily addressed in Lilly's responses.

Sincerely,

Frederick C. Mills, Ph.D.

Memo

To: Laurie Norwood,M.Sc, DMP,Office of Compliance, CBER

Cc Gibbes Johnson, Ph.D., DTP, OTRR, CBER; Barry Cherney, Ph.D., Deputy Director, DTP, OTRR, CBER; Amy Rosenberg, M.D., Director, DTP, OTRR, CBER

From: Frederick C. Mills, Ph.D. Staff Scientist, DTP, OTRR, CBER

Date: 9-21-01

Subject: Disposition of rhAPC Drug Substance lots affected by clean steam conductivity excursion at -------- ----------

Background : -------- 483 Observation 1, and Discussion from the -------- Draft EIR by Laurie Norwood

1. A thorough investigation of the Clean Steam System failure was not conducted for its impact on quality of the product. The Clean Steam System for the ---------- ---------- failed the USP conductivity test 50% of the days (total of 30 days) the system was monitored from March 23 to June 2, 2000. Final drug substance rhAPC lots affected by this excursion are ----------. (written by LPN)

Conductivity excursions/investigation

The clean steam conductivity data from 1998 to 2000 (Exhibit LPN-01) illustrates a trend of conductivity failures as well as USP stage 2 and 3 conductivity testing of the clean steam system from March 23 to June 2, 2000. Conductivity values as high as 4.79 µS/cm were reported (page 6 of the data, Exhibit LPN-01.) In 1998, most of 1999, and after June 2, 2000 the clean steam conductivity values were on average less than 1 µS/cm at USP stage 1 testing. Environmental Excursion ER-47-0059 was raised at the onset of the excursions. ----------) explained that once a trend was noted the ER was raised to the level of an Investigation Event Report (----------, Exhibit LPN-01.) The investigation included an evaluation of the system and source water by the consulting firm ---------- and an increased monitoring of the Clean Steam System until the system tested normal for conductivity, passing USP stage 1 testing.

---------- summarized their results in a letter to -------- on June 6, 2000 (Exhibit LPN-01, last 4 pages of ----------.) The summary is as follows:

- The investigation of---------- contamination in the clean steam system was difficult
- The contamination began in November 1999 (do see trend of USP stage 3 testing at that time) at the same time water use dramatically expanded. High demand placed a burden on the purified water system. High volume operation tends to overrun the water processing technologies resulting in degraded water quality.

- Clean steam ---------- levels range from <10ppb on surface water to approx. 200-300 ppb in April. ---------- is only detected in the clean steam when the system is on ---------- water. ---------- has not been detected in the purified water, RO or CDI product at any time.
- There is no explanation yet as to how the ---------- gets into the clean steam product water, and the surface ---------- data does not clarify the issue.
- ---------- levels do increase after the --------- system when the ---------- addition is activated in the ---------- system in conjunction with the source water from the ------ The ---------- is suspected of being ferried through the water purification process as ----------(April 9, 200 letter, Exhibit LPN-01)
-

--------recommended the following: The existing water ---------- system is not capable of handling the capacity of water through put, given the existing quality of source water (possible elevated levels of ---------- are most easily removed by ----------) (pg 2 of 3, 4/19 letter, Exhibit LPN-01). Therefore, given the requirements, a ---------- unit should be installed in place of the current ----------. The new ---------- unit was replaced on June 6, 2000 (Exhibit LPN-02). Clean steam monitoring data were within specifications for all of 2000 and up to May 2001.

Product impact/Discussion with management

Clean steam is used to sterilize product contact surfaces of equipment such as bioreactors, transfer piping, tanks, and chromatography rigs used in the production of rhAPC. The final drug substance rhAPC lots affected by this excursion are -------- -------, ----------. Lot ------- was made from lot ---------- manufactured March 2 to April 12, 2000 (Exhibit LPN-03, pg. 6). Lots ------- and ----- were made from lot ---------- ---------- manufactured May 26 to June 4, 2000 (Exhibit LPN-03, pgs. 7&8).

I (Laurie Norwood) asked ---------- if Lilly was intending to market the affected lots. He said that it was Lilly's intentions to market all lots that meet final specifications. I pointed out that Lot --------- was made prior to the conformance lots and that he should contact CBER with regard to distributing any lots that were made prior to their validation runs.

Summary of Characterizaiton and Stability on rhaPC Drug Substance Lots ---------, ----------

Lot Release and Additional Characterization

Data in the BLA (Drug Substance section, pp. 743-746) includes Lot Release Characterization for Lots ----------. The Pass Criterion for the following identity tests is "Pattern Compares favorably with the reference standard.."

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The data for Lots ---------- all fall well within these lot release criteria, and show values consistent with the other full-scale commercial lots described in the BLA (----------).

Additional characterization beyond lot release includes :

[

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In these characterizations, Lots ---------- show values consistent with the other full-scale commercial lots.

Drug Substance Stability (provided in Amendment 20, at the request of Fred Mills)

---------- month stability data has been provided for lots -------, and -------, as well as -- month stability data for lot ------. These stability data consist of measurements at --- ^{0}C and --- ^{0}C for :

---------- ----------

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For the time periods provided, lots ---------- have remained within the stability criteria, and data for these lots are consistent with data for other Drug Substance lots on stability (----------produced at --------, and ----------produced at Lilly, ----------).

Stability Data for Drug Product Lots Derived form Drug Substance Lots ------- and -------- (from Amendment 20, as requested by Fred Mills)

Drug Product Lot ---------(5 mg vials) has been derived from Drug Substance Lot -------, and Drug Product Lots --------- (20 mg vials) and ------- (20 mg vials) have been derived from Drug Substance Lot -------. Amendment

Parameters measured in the Drug Product stability program are:

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Stability data for -- months at -- ^{0}C and -- months at --- ^{0}C and --- ^{0}C is provided for Lot ---------, with -- month data being provided for Lots ---------- and ----------. For the times provided, these lots remain within the stability criteria, and the data are consistent with other Drug Product lots on stability.

Summary

Data has been reviewed for Drug Substance lots ----------, which were made during the Clean Steam conductivity excursion at -------- ---------- during the time period March 23-June , 2000. Lot release data, extended characterization data, Drug Substance stability data, and stability data for Drug Product lots derived from two of these Drug Substance lots are within specifications and consistent with data for other lots made outside the Clean Steam excursion. This review supports the release of Drug Product made from Drug Substance lots ---------- for commercial distribution.

Frederick C. Mills, Ph.D.